REMARKS

I. Status of th Application

Claims 60, 66-71, and 73-96 have been under examination. In the Amendment under 37 C.F.R. § 1.116 filed January 4, 2003, Applicants submitted new claims 97-104. Support for the new claims is described at pages 2 and 3 of that Amendment. The Office did not enter these new claims. (Advisory Action of April 22, 2003.)

In the attached Request for Continued Examination, Applicants respectfully request entry of claims 97-104. Thus, claims 60, 66-71, and 73-104 are now pending.

II. Claims 60, 66-71, 73-88, and 91-94 Are Nonobvious over Chidlow in view of Cravioto

The Office rejects claims 60, 66-71, 73-88, and 91-94 under 35 U.S.C. § 103(a) as allegedly obvious over Chidlow et al. ("Chidlow"; U.S. Patent No. 4,141,970) in view of Cravioto et al. ("Cravioto"; *J. Infect. Dis.* 163: 1247-55 (1991)). Applicants traverse this rejection.

The Office uses Chidlow as the primary reference in this rejection, contending that Chidlow teaches administering a composition comprising the EHEC strain 0157 to a milk-producing animal, and administering the antibodies generated from the milk-producing animal to its offspring. (Attachment to Advisory Action at pages 3-4.) The Office also relies on Chidlow for teachings of different types of food animals such as cows, pigs, and sheep, and for teachings of the raising, breeding, and preparing of animals for food. (*Id.* at page 4.)

The Office relies on Cravioto for a suggestion that the O157 strain of *E. coli*, mentioned in Chidlow produces the intimin protein. From this, the Office concludes that "the antibodies of Chidlow et al. obviously comprised intimin due to an enriched

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composition of *E. coli* that produce intimin." (*Id.* at page 3.) The Office also contends that Cravioto teaches anti-intimin antibodies that "were able to block binding to mammalian cells *in vitro*," protection of offspring from infection by maternal anti-intimin antibodies, and purification of intimin by gel electrophoresis (according to Figure 6, and the text of page 1251 of Cravioto). (Office Action of August 15, 2001, at page 15.) The Office acknowledges that Cravioto does *not* teach "administering of anti-intimin antibodies to a host to generate anti-intimin antibodies," as Applicants claim. (Office Action of October 4, 2003, at pages 4-5.)

Applicants respectfully submit that this rejection does not set forth a *prima facie* case of obviousness. First, the combination of these references does not teach or suggest all of the elements of Applicants' independent claims 60, 73, and 76. Second, the teachings of Chidlow and Cravioto as a whole do not motivate one of ordinary skill in the art, knowing nothing of Applicants' disclosure, to combine their teachings. Third, the teachings of those references as a whole do not provide one of ordinary skill in the art with a reasonable expectation of success in performing the claimed invention. In addition, Applicants respectfully submit that some of the Office's contentions regarding the teachings of Chidlow and Cravioto are not supported with the necessary substantial evidence or scientific reasoning according to the Federal Circuit's standards of *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001) and *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

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A. The Teachings of Chidlow and Cravioto

Applicants respectfully submit that some of the Office's characterizations of the teachings of Chidlow and Cravioto are not supported by the disclosures of those

references. Moreover, in responding to Applicants' prior arguments, the Office contended that "one cannot show obviousness by attacking references individually where the rejections are based on combinations of references." (Attachment to Advisory Action of April 22, 2003, at page 2.) This standard does not mean that one cannot point out deficiencies in each of the prior art references. Rather, it stands for the proposition that references must be read for what they fairly teach in combination with the prior art as a whole. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1987 (Fed. Cir. 1986.) Thus, it is proper to consider what each reference teaches as a whole in order to properly appreciate what the combination of references teaches to those of ordinary skill in the art.

Chidlow discloses methods of administering endotoxins derived from several different *E. coli* strains to pregnant animals in order to provide immunoprotection to their newborn young. (Chidlow at Abstract; col. 1, lines 50-63; and col. 2, lines 43-49.) Endotoxins are not proteins like intimin, but are lipopolysaccharide molecules. Endotoxins reside in the outer membranes of many Gram-negative bacterial strains and induce inflammatory responses in infected animals. (Exhibit A provides some background technical information about the structure and the immunogenic and pathogenic function of endotoxins.) Although Chidlow permits the inclusion of other potentially antigenic cellular materials, such as exotoxins and "cell debris," Chidlow emphasizes that "endotoxins are of primary importance in obtaining the desired immunological effect while the exotoxins and cell debris are not." (Chidlow at col. 2, line 59, to col. 3, line 7; see Exhibit A for background information on exotoxins.)

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Moreover, the other data in Chidlow supports completely Chidlow's focus on endotoxins. For example, Chidlow's working examples describe methods of obtaining free endotoxins from *E. coli* cells. These examples include subjecting cells to extreme heat or specifically precipitating endotoxin materials. (Chidlow at col. 3, lines 37-46, and at Examples 4, 6, 8, and 9.)[1] In Chidlow's Example 8A, the endotoxins are prepared by heating bacterial cultures at 125 °C for 2 hours. Chidlow explains at col. 4, lines 30-34, that the endotoxins fed to animals in its working examples were prepared by a similar heat-sterilization procedure. (See also Chidlow at col. 3, lines 37-46, noting that the procedure involves heating to over 100 °C.) Chidlow further comments that, when such endotoxin compositions are given to animals, "[t]he passive immune status of the offspring is accordingly much enhanced, and their susceptibility to infection correspondingly much reduced." (Chidlow at col. 4, lines 5-22, and Examples 1-3 and 5.)

In contrast, Chidlow is entirely silent as to intimin, or any other adherence factor. . Moreover, because these components are both structurally and functionally distinct, one of ordinary skill in the art would not confuse an endotoxin or exotoxin with an adherence factor such as intimin. (See Exhibit A.) While Office is correct that EHEC *E. coli* strain O157, among those that Chidlow discloses, was known in the art at the time

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[1] Note that Chidlow's Examples 6-9 apparently were originally numbered 1-4, given the way in which they refer to each other. For instance, Example 8A refers to an "assay procedure of Example 2," in which an antibody titre is determined. However, that protocol is described in Example 7. Similarly, Example 9 refers to "the procedure A in Example 3," containing a "final culture." That "final culture" however, is discussed in Example 8A, not in Example 3.

of Applicants' invention to produce intimin,[2] this does not take away from Chidlow's teaching that endotoxins are of primary importance in immunologically protecting newborn animal patients from challenge with bacterial pathogens. (Chidlow at col. 2, line 59, to col. 3, line 7.) Indeed, the teaching one takes from Chidlow is that administering endotoxins antigens to sows provided immune protection to their newborn young. (Chidlow at col. 3, line 47, to col. 4, line 22; see also Chidlow at examples 1-3.)

Nevertheless, the Office contends that Chidlow's compositions or antibodies "obviously comprised intimin due to an enriched composition of *E. coli* that produce intimin." (Attachment to Advisory Action at page 3.) In other words, the Office contends that because Chidlow discusses an *E. coli* strain that produces intimin, one of ordinary skill in the art would believe that Chidlow's endotoxin compositions include active intimin antigens. The Federal Circuit requires that such conclusions be supported by substantial evidence or scientific reasoning according to the standards of *In re Zurko* and *In re Lee*. 59 U.S.P.Q.2d at 1693; 61 U.S.P.Q.2d at 1430. The Office has provided no evidence or reasoning to support its conclusion that Chidlow's compositions could contain intimin antigens, or that Chidlow's antibodies could include anti-intimin antibodies.

In fact, Applicants herein provide evidence that contradicts this conclusion. Specifically, as noted above, Chidlow's procedure of obtaining polysaccharide endotoxins is to heat cells to 100-125 °C for 2 hours. This high level of heat is likely to irreversibly denature many cellular proteins, such that they could no longer function as

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[2] The Office relies upon Cravioto for that teaching, though Cravioto does not discuss EHEC strains.

suitable antigens. For example, those in the art recognize that proteins are fragile molecules designed to function optimally at 37 °C. They may become irreversibly denatured if exposed to extremes of temperature. (See Exhibit B; commenting that "protein solutions should not be exposed to extremes of pH, high temperatures, organic solvents, or any other condition that might promote denaturation.") Thus, the evidence suggests that one of ordinary skill in the art would not conclude that Chidlow's endotoxin compositions include active intimin antigens, or that anti-intimin antibodies necessarily contributed to the success of Chidlow's method.

In summary, Chidlow explicitly teaches that one should give endotoxins to pregnant animals to provide immune protection to their newborn offspring, and that, while other cellular materials could be included in the endotoxin compositions, these are of little or no immunologic importance. (Chidlow at col. 2, line 43, to col. 3, line 7, and at col. 4, lines 5-22.) The Office has not shown sufficient evidence or reasoning to demonstrate that there is anything implicit in Chidlow's data that suggests that intimin could also be immunologically important.

As with Chidlow, Applicants respectfully submit that the teachings in Cravioto are not as broad as the Office contends. Cravioto investigates the notion that breast milk may provide some degree of protection to newborns from infectious agents to which the mother has previously been exposed. Cravioto and co-authors were interested in determining how breast-feeding helps to protect human newborns against enteropathogenic *E. coli* (EPEC) infection by determining whether or not there are any specific factors in breast milk that enhance the immune protection of newborns. (Cravioto at page 1247, introductory text at cols. 1-2.)

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Cravioto and coauthors obtained breast milk from 14 Mexican women who had previously been exposed to EPEC infection, and accordingly, would have produced antibodies related to that prior exposure. (Cravioto at p. 1248, col. 1.) The authors took secretory IgA (sIgA) antibodies and oligosaccharide-enriched fractions from the milk, and tested those components to determine whether they could inhibit adherence of EPEC strains to mammalian HEP-2 cells in culture. (Cravioto at "Materials and Methods," page 1248, col. 1, to page 1249, col. 2; "Results" at pages 1250-2; Figures 5-7.)

But, their conclusions from this data are quite tentative. From their results as a whole, Cravioto and coauthors concluded that *both* sIgA antibodies and oligosaccharides "*could be* two of the most important protective fractions" in the milk of mothers who have been exposed to prior EPEC infection. (Cravioto et al. at page 1253, col. 2, last complete paragraph, emphasis added.) The authors also pointed out that "[t]he specific inhibitory capacity of total breast milk against EPEC strains infecting infants at an early age is probably due to the presence of *many factors*, including the ones studied here." (*Id.*; emphasis added.)

Indeed, as Cravioto and coauthors implicitly recognize, because they were working with milk from mothers exposed to the natural bacterial infections, there were likely other types of antibodies in that milk, such as anti-endotoxin antibodies, or antibodies against other bacterial toxins or secreted proteins. Cravioto et al. did not test for the presence of these other antibodies. Nor did they consider how other antigens could have played a role in protecting infants from infection.

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B. There is No Motivation to Combine the Teachings of Chidlow and Cravioto

As mentioned above, motivation to combine or modify references turns on whether the combination is *desirable*, based on the teachings of the cited references in view of the art as a whole. *Winner v. Wang*, 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000) M.P.E.P. § 2143.01. Taken together, the teachings of Chidlow and Cravioto do not provide sufficient desire for one of ordinary skill in the art, knowing nothing of Applicants' disclosure, to produce the claimed invention.

As discussed at length above, Chidlow teaches that administering *endotoxins* leads to a protective immune response in newborns and presents data to support that teaching. Further, by commenting that "endotoxins are of primary importance in obtaining the desired immunological effect while the exotoxins and cell debris are not," Chidlow teaches away from administration of intimin. (Chidlow at col. 2, lines 59-66.) Indeed, a reference showing that a particular antigen provides immunoprotection does not lead one of ordinary skill in the art to replace that antigen with a different antigen.

Cravioto cannot motivate one of ordinary skill in the art to replace the endotoxin antigens of Chidlow with "enriched or purified" intimin antigens. Again, Cravioto concludes that antibodies against EPEC intimin and various oligosaccharides are only two of "many factors" important in protecting newborns from infection. (Cravioto at p. 1253, col. 2.) Further, Cravioto and coauthors did not test breast-milk antibodies for recognition of other antigens such as endotoxins or secreted proteins. Therefore, Cravioto adds nothing to the teachings of Chidlow about the benefits of administering endotoxins.

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In summary, this combination of references, in light of the prior art as a whole, teaches that many factors may help to protect newborns from infection, and that endotoxins actually enhance immune protection. Thus, the combined teachings do not provide any suggestion or motivation to replace endotoxin compositions with "enriched or purified intimin" as set forth in Applicants' claims. The Office has not met this prong of the *prima facie* case.

C. Chidlow and Cravioto Do Not Provide One of Ordinary Skill in the Art with a Reasonable Expectation of Success in Performing the Claimed Methods

Further, the combination of Cravioto and Chidlow does not provide a reasonable expectation of success in performing Applicants' claimed methods. Again, Chidlow expressly concludes that immune protection of newborns is enhanced when they are given anti-endotoxin antibodies. (See Chidlow at col. 2, line 43, to col. 3, line 7, and at col. 4, lines 5-22.) And, as developed above, nothing in Chidlow suggests that antibodies to some other factor significantly contributed to the successful immune protection. Moreover, as discussed previously, Chidlow's endotoxin compositions came from high heat-treated cells, a process that generally denatures bacterial proteins. Further, Chidlow's endotoxin compositions contained a high concentration of endotoxins, as tested by the assay procedure and reagents described in its Examples 6 and 7. Thus, everything in Chidlow points to the endotoxins as the immune-enhancing agent, and nothing in Chidlow suggests a contribution by another antigen.

Cravioto does not overcome the deficiency of Chidlow. Cravioto merely suggests that intimin is one of many factors that may be important for protecting against infection. Moreover, the design of Cravioto's experiments introduced many possible factors. The

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test subjects had been exposed to actual pathogenic EPEC infections, and therefore to all EPEC antigens. One cannot determine what role was played by those other antigens. Cravioto makes no explicit, or even implicit, suggestion that administering "enriched or purified intimin" alone would provide passive immune protection.

D. Chidlow and Cravioto Do Not Teach or Suggest "Enriched or Purified Intimin"

Finally, even if there were sufficient motivation to combine the teachings of Chidlow and Cravioto, that combination does not teach "enriched or purified intimin." Because Chidlow is silent as to intimin, it cannot contain any express teaching of enriching or purifying intimin. Nor does Chidlow's disclosure inherently suggest enriching or purifying intimin, because, as discussed above, it relates to endotoxins and teaches that other "cell debris" is of little immunologic importance. (Chidlow at col. 2, line 59, to col. 3, line 7.) Further, as discussed above, the Office has not provided any reason to suppose that Chidlow's compositions include active intimin antigens or anti-intimin antibodies. Thus, any teaching of "enriched or purified intimin" could only come from Cravioto.

The Office contends that Figure 6 of Cravioto, and the text associated with that figure, teaches "purified intimin." (Office Action of August 15, 2001, at page 15, citing Cravioto at Figure 6, and page 1251.) However, Applicants respectfully submit that this is in error. Figure 6 presents an SDS-PAGE analysis of an outer-membrane protein fraction from *E. coli*. (*Id.*) SDS-PAGE is a method of analysis by electrophoresis and not a method of protein purification. SDS-PAGE gel does not "purify" proteins in any way that is of practical value to one of ordinary skill in the art interested in subsequently

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using the proteins. First, the method employs only very minute quantities of proteins. Second, proteins subjected to SDS-PAGE are first boiled for about 5 minutes in a denaturing solution so that they are completely unfolded and all disulfide bonds are broken. As a result, proteins separated by SDS-PAGE are usually totally unable to re-fold into any practically useful structure. Thus, even if one could isolate intimin from an SDS-PAGE gel, the protein that one would obtain would be very unlikely to be of any use as an antigen generating anti-intimin antibodies that can block binding to mammalian cells, for example. (Exhibit C provides a description of SDS-PAGE.)

Cravioto, in combination with Chidlow and the art as a whole, also does not fairly teach or suggest methods of making or administering "enriched" intimin. At best, Figure 6 shows how to obtain a fraction of outer-membrane proteins, but none of these proteins are "enriched" in any way because they are simply isolated from *E. coli* in their natural concentrations. In contrast, Applicants' enriched proteins are prepared, for example, by overexpressing intimin in laboratory bacterial strains. (See Examples II and III, at pages 34-38 of the specification.) Nor does Cravioto inherently suggest enriching intimin protein. Its disclosure as a whole relates to immunoglobulins and oligosaccharides present in human milk after exposure to EPEC pathogens in their natural, disease-producing state.

In conclusion, the Office has not met any of the three prongs of the *prima facie* obviousness test. Therefore Applicants respectfully request the withdrawal of this rejection.

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III. Rejection of Claims 60, 66-71, and 73-96 over Dougan in view of Chidlow

The Examiner rejected claims 60, 66-71, and 73-96 under 35 U.S.C. § 103(a) as allegedly obvious over Dougan et al. ("Dougan"; U.S. Patent No. 5,747,293) in view of Chidlow. Applicants traverse this rejection.

The combination of Dougan and Chidlow also fails to present a *prima facie* case of obviousness. First, there is no motivation or desire for one of ordinary skill in the art to combine the teachings of these references. Second, if one of ordinary skill in the art were, nevertheless, to combine them, that combination would not include all of the elements of Applicants' claims. Third, the teachings of Dougan and Chidlow provide no reasonable expectation of success in performing Applicants' claimed methods. Finally, Applicants respectfully note that the Office does not support some of its contentions about Chidlow and Dougan with any substantial evidence or scientific reasoning.

A. There is No Motivation to Combine Dougan and Chidlow

In this rejection, the Office relies on Chidlow for a teaching of generating antibodies against EHEC in a host animal for the protection of its newborn offspring. (Office Action of August 15, 2001, at pages 17-18.) The Office contends that Dougan teaches "a conserved, receptor associated portion of intimin for administration and induction of an immune response that will block binding and treat infection," citing Dougan at col. 2, lines 43-44. (*Id.*)

This rejection is not based upon the teachings of Chidlow and Dougan as a whole. First, Chidlow, as in detail above, says nothing about intimin and instead teaches that passive immune protection may be obtained by administering endotoxin compositions to generate anti-endotoxin antibodies. Indeed, Chidlow's complete focus

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upon endotoxins, and its demonstration that free endotoxin compositions actually enhance passive immunity, teach away from administering "enriched or purified" intimin compositions as Applicants claim.

Dougan does not overcome the deficiencies of Chidlow. First, contrary to the Office's contentions, Dougan does not discuss administration of antibodies, treatment or immunoprotection. Instead, Dougan's disclosure is focused almost exclusively on the use of the antibodies for detecting EPEC or EHEC cells in samples. (Dougan at Abstract; col. 1, lines 3-8; col. 3, line 48, to col. 4, line 42; Examples 1-4.) The Office's contention that Dougan teaches administering intimin for therapeutic purposes comes from a single phrase in Dougan stating that antibodies that recognize EPEC intimin but do not recognize EHEC intimin "will therefore be useful in both the detection and/or treatment of EPEC infection." (Dougan at col. 2, lines 41-44.) But this phrase does not bear up to the weight the Office gives it.

First, EPEC and EHEC are not the same, and the claims here require antibodies that block the binding of EHEC to mammalian cells. Recognition of EHEC intimin is a requirement for blocking the binding of EHEC to mammalian cells. Thus, antibodies that recognize EPEC intimin but do not recognize EHEC intimin simply cannot be used in Applicants' methods.

Second, Dougan simply makes this assertion without any data or other support for it. It's working examples describe only obtaining polyclonal and monoclonal antibodies against a portion of the intimin protein using standard rabbit inoculation and mouse hybridoma techniques, and the data show that its monoclonal anti-EPEC intimin

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antibodies are capable of recognizing EPEC bacteria cells in solution. (Dougan at Examples 1-4.)

Dougan cannot motivate one of ordinary skill in the art to turn away from Chidlow's teachings and administer enriched or purified intimin as Applicants claim.

B. Dougan and Chidlow Do Not Teach or Suggest All of the Elements of Applicants' Claims

Moreover, the combination of Chidlow and Dougan fails to teach or suggest antibodies that "block binding of enterohemorrhagic *E. coli* to a mammalian cell," as required in all of Applicants' claims. Again, Applicants submit that this teaching cannot come from Chidlow because it is silent as to intimin. Further it provides no suggestion that anti-endotoxin antibodies could block this binding.

Dougan does disclose the approximately 280-amino acid carboxy-terminal region of EPEC and EHEC intimin for "use in detection." (Dougan at col. 1, lines 3-8; col. 3, line 48, to col. 4, line 42; Abstract.) While it is correct that this part of intimin is involved in mammalian cell recognition, Dougan's disclosure indicates selection of the 280-amino acid carboxy-terminal region of intimin was chosen as an antibody target because this region of intimin is the most exposed and accessible for use in detection. (Dougan at col. 2, lines 6-24.)

Further, not all antibodies that bind to this 280 amino-acid portion of intimin would block binding of bacteria to mammalian cells. Only the final 192 amino-acids of that region are implicated in mammalian cell adherence, according to Dougan's disclosure. (Dougan at col. 2, lines 6-7.) In fact, Dougan's antibodies did not recognize the final 149 amino acids of the EPEC intimin protein. (Dougan at col. 6, line 49, to col. 7, line

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1.) Again, Dougan's antibodies do not recognize EHEC intimin, as Applicants' claimed antibodies must do. The ability of an antibody to block binding of intimin to cells also depends on its affinity for intimin. Thus, it is completely uncertain whether Dougan's antibodies would actually block binding of EPEC to mammalian cells, let alone to the claimed EHEC.

C. There is No Reasonable Expectation of Success in Performing th Combination of Chidlow and Dougan

Finally, there is also no reasonable expectation of success. To reiterate, Chidlow, discusses only endotoxin compositions, and nothing suggests that its compositions include active intimin antigens or that intimin contributed in any way to the success of Chidlow's immune protection protocol. (See Part B above.) Thus, Chidlow does not suggest that intimin antigens could be protective.

Dougan does not bridge this gap in Chidlow's teachings. Dougan simply asserts, without any supporting discussion or data, that antibodies that recognize EPEC intimin but do not recognize EHEC intimin "will therefore be useful in both the detection and/or treatment of EPEC infection." (Dougan at col. 2, lines 41-44.)

First, as previously explained, EPEC and EHEC are not the same, and the claims here require antibodies that block the binding of EHEC to mammalian cells. Recognition of EHEC intimin is a requirement for blocking the binding of EHEC to mammalian cells. Thus, antibodies that recognize EPEC intimin but do not recognize EHEC intimin simply cannot be used in Applicants' methods.

Second, all of Dougan's working examples relate merely to using anti-intimin antibodies to detect EPEC in samples.

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Third, as discussed above, its anti-EPEC intimin antibody does not bind to the final 149 amino acids of intimin, which constitute the majority of the cellular binding region of EPEC intimin. Thus, there is no indication that Dougan's EPEC-specific antibodies would actually block binding of EPEC to mammalian cells, while, because they don't recognize EHEC-intimin, they certainly could not block EHEC's binding to mammalian cells.

Finally, nothing in Dougan suggests that, if one were actually to administer enriched or purified intimin to an animal, the anti-intimin antibodies would provide any degree of immune protection.

Given the deficiencies of Dougan and Chidlow, Applicants conclude that the Office improperly bases this rejection, by hindsight, on Applicants' disclosure. *See, e.g., In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-2 (Fed. Cir. 1988). It appears to Applicants that the Office has picked and chosen only so much of Dougan as would support this rejection without considering that Dougan as a whole is focused upon using antibodies for detection and provides no explanation of how any anti-intimin antibodies could be used successfully in any treatment protocol. *See In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Therefore, the Office has not met any of the three prongs of a *prima facie* case of obviousness, and Applicants respectfully request the withdrawal of this rejection.

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IV. Applicants Methods Have Shown Unexpected Results and Achieved Commercial Success

As fully developed above, the Office has not made out a *prima facie* case of obviousness with either of the rejections. For this reason alone, Applicants submit that all of the pending claims are allowable. Nonetheless, to facilitate prosecution, and not in acquiescence, Applicants also provide information and data supporting "objective indicia" of nonobviousness.

A. Unexpected Results: The Dean-Nystrom Abstract

Applicants previously presented to the Office an abstract from Dean-Nystrom et al. as evidence of unexpected results. The Preliminary Amendment of May 24, 2001, at pages 9-10, describes the Dean-Nystrom experiment in detail.

In Dean-Nystrom's experiment, a group of pregnant sows were vaccinated twice with a purified EHEC intimin protein. This resulted in a change in the colostral titers of anti-intimin antibodies from a base-line of $\leq$100 to $\geq$100,000. Their piglets were challenged with a strain of EHEC after suckling for up to eight hours. Another group of pregnant sows were not vaccinated, and their piglets were challenged as controls, again, after up to eight hours of suckling. Nearly all of the 27 control piglets showed A/E bacteria in the large intestine and $\geq 10^6$ CFU of inoculum bacteria per gram of cecal tissue. In contrast, only 5 of the 22 piglets whose mothers had been given intimin showed either A/E bacteria or $\geq 10^6$ CFU/g. Thus, these results demonstrate successful passive immune protection, in which patients were protected from challenge with EHEC bacteria.

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The Office asserts that the results presented in the Dean-Nystrom abstract are not commensurate in scope with the invention as claimed. First, the Office asserts that the results are limited to pigs. (See the Office Action of August 15, 2001, at page 8.) Applicants previously acknowledged that the hosts and patients of Applicants' claims comprise several animals, including humans. (Amendment filed January 29, 2002, at pages 8-9.) However, the pig model was chosen for the Dean-Nystrom experiment largely because the pig immune system it is a *good and accepted model* in the art for the human immune system, among others. (*Id.*; *see also* Applicants remarks filed January 29, 2002, at pages 8-9, and the exhibit attached thereto.) Applicants cannot ethically perform experiments like those of Dean-Nystrom on humans due to Food and Drug Administration regulations.

In addition, the Federal Circuit has repeatedly maintained that a showing of unexpected results for a species in a claimed genus is sufficient to rebut a *prima facie* case of obviousness throughout the entire scope of the claim when one skilled in the art can reasonably conclude that similar results would be obtained for other members of the genus. *See, e.g., In re Chupp*, 816 F.2d 643, 646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987); *In re Clemens*, 622 F.2d 1029, 1036, 206 U.S.P.Q. 289, 296 (CCPA 1980). These holdings are particularly relevant here, as the pig is a commonly used model of other immune systems such as that of humans. (Amendment filed January 29, 2002, at pages 8-9, and exhibit attached thereto.)

Second, the Office contends that the Dean-Nystrom abstract is not applicable to non-colostral antibodies with titers lower than 100,000. However, Applicants previously

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pointed out that it would be difficult to test different sources and titers because this experiment relies on the natural physiological responses of the sows to the vaccine.

In summary, Office has not provided credible factual evidence according to the standards of *Zurko* and *Lee* to support its contentions about the Dean-Nystrom abstract. Instead, the Office Action of August 15, 2001, merely asserts that the abstract recites antibodies from colostrum in a particular titer and asserts that the instant claims are not limited to colostral administration or a to particular titer. (See the Office Action of August 15, 2001, at page 8, and the Office Action of October 4, 2002, at pages 6-7.)

B. Commercial Success: Licensing of the Invention

In the Preliminary Amendment filed May 24, 2001, Applicants also provided evidence of commercial success, through a license by Biosynexus, Inc. This licensee has licensed the instant invention merely from the strength of the disclosure and the underlying research, and prior to the issuance of any claim. Thus, by definition, this license is commensurate with the scope of the claims as a whole.

It is well known that the commercialization of biotechnology methods and products is often exceedingly long and requires the approval of one or more regulatory agencies. The instant license demonstrates commercial success on its face because the licensee has recognized with its pocketbook the value of the disclosed technology at an early stage and will absorb much of the very high costs associated with commercial development and regulatory approval of the method. Indeed, the purpose of a license is to bring the subject of an invention to market. Thus, by definition, the license of a claimed technology at the stage of development of the claimed technology is the very essence of commercial success of a product.

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CONCLUSION

In summary, Applicants hereby submit that claims 60, 66-71, 73-88, and 91-94 are non-obvious over Chidlow and Cravioto, and that claims 60, 66-71, and 73-96 are non-obvious over Chidlow and Dougan. Further, new claims 97-104 are also non-obvious over these publications. Thus, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge all required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: August 4, 2003

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